NDA 20-764/SCF-006
NDA 20-241/SLR-014

SEP 8 2000

Glaxo Weilcome Inc.
Attention: Elizabeth A. McConnell, PhanmD.
Project Director, Regulatory Affairs
Five Moore Drive; P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Dr. McConnell:

Please refer to your supplemental new drug applications dated December 1, 1999 (NDA 20-764/8-006) and August 8, 2000 (NDA 20-241/S-014), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Chewable Dispersible Tablets and Lamictal (lamotrigine) Tablets.

We acknowledge receipt of your submissions to NDA 20-764/S-006 dated May 8, 2000, June 14, 2000, August 8, 2000, and September 7, 2000. We also acknowledge receipt of your submission to both supplemental applications dated August 24, 2000.

These supplemental new drug applications provide for the following:

NDA 20-764/S-006	A new lower 2mg dosage strength of Lamictal Chewable Dispersible Tablets and corresponding labeling changes
NDA 20-241/S-014	Labeling changes to incorporate new information into the package insert given the availability of the 2mg dosage strength of Lamictal Chewable Dispersible Tablets

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (immediate container and carton labels submitted May 8, 2000).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format -NDAs (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-764/S-006 and NDA 20-241/S-014." Approval of these submissions by FDA is not required before the labeling is used.

In addition, we note that your supplemental new drug applications (NIDA 20-241/SLR-010 and NDA 20-764/SLR-003), submitted on February 8, 1999 as "Special Supplement: Changes Being Effected, Labeling" for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets remain under review.

Supercede

We have reviewed the content of the following supplements submitted as "Special Supplement: Changes Being Effected, Labeling,"and we note that these changes have been incorporated in the enclosed labeling text. Therefore, the supplemental applications listed below have been superceded, and will be retained in our files with no further action.

Supplement Number:	Date Submitted:
NDA 20-241/SLR-013	May 19, 2000 (initial submission) June 30, 2000 (amendment)
NDA 20-764/SLR-007	May 19, 2000 (initial submission) June 30, 2000 (amendment)

Dissolution Methodology and Specification

We note that, in your September 7, 2000 submission, you agreed to the Agency's proposed dissolution methodology and specification for the 2mg dosage strength of Lamictal Chewable Dispersible Tablet as stated in our March 29, 2000 action letter and as discussed during the September 5, 2000 teleconference between Jacqueline Ware of this Division and Glaxo representatives. This dissolution methodology and specification is that which is already approved for other strengths of Lamictal Chewable Dispersible Tablets.

Phase 4 Commitments

We acknowledge that with this approval, all Phase 4 Commitments, described in our August 24, 1998 approval letter for Lamictal Chewable Tablets, have been fulfilled.

Promotional Materials

Please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Other

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MIEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MID 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

LAMICTAL®
(lamotrigine)
Tablets

PRODUCT INFORMATION

LAMICTAL®
(lamotrigine)
Chewable Dispersible Tablets

SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3% (3/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

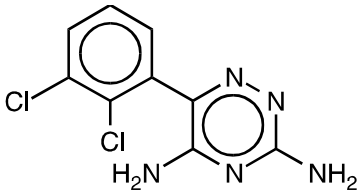
BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC PATIENTS THAN IN ADULTS, IT BEARS EMPHASIS THAT LAMICTAL IS APPROVED ONLY FOR USE IN PEDIATRIC PATIENTS BELOW THE AGE OF 16 YEARS WHO HAVE SEIZURES ASSOCIATED WITH THE LENNOX-GASTAUT SYNDROME (SEE INDICATIONS).

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY 1) COADMINISTRATION OF LAMICTAL WITH VALPROIC ACID (VPA), 2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR 3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

DESCRIPTION: LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg (peach), 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only); ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only).

LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The tablets contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

CLINICAL PHARMACOLOGY:

Mechanism of Action: The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of LAMICTAL, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Pharmacological Properties: Although the relevance for human use is unknown, the following data characterize the performance of LAMICTAL in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT_3 receptor (IC_{50} = 18 μM). It does not exhibit high affinity binding (IC_{50}>100 μM) to the following neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α_1, α_2, and β; dopamine D_1 and D_2; γ-aminobutyric acid (GABA) A and B; histamine H_1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT_2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC_{50} = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, serotonin, or aspartic acid (IC_{50}>100 μM).

Effect of Lamotrigine on N-Methyl d-Aspartate (NMDA)-Mediated Activity: Lamotrigine did not inhibit NMDA-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM.

Folate Metabolism: In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis (see PRECAUTIONS: Pregnancy). Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys: Lamotrigine was found to accumulate in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine (see Drug Disposition below). However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

Pharmacokinetics and Drug Metabolism: The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are summarized in Tables 1 and 2.

Table 1: Mean* Pharmacokinetic Parameters in Adult Patients With Epilepsy or Healthy Volunteers

Adult Study Population	Number of Subjects	t_{max}: Time of Maximum Plasma Concentration (h)	$t_{½}$: Elimination Half-life (h)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs)†:				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)
Patients taking EIAEDs + VPA:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients taking VPA only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Healthy volunteers taking VPA:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)

*The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and Cl/F and between 30% and 70% for t_{max}. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

†Examples of EIAEDs are carbamazepine, phenobarbital, phenytoin, and primidone.

The apparent clearance of lamotrigine is affected by the coadministration of AEDs. Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs, including carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical experience is derived from this population.

VPA, however, actually decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine), whether given with or without EIAEDs. Accordingly, if lamotrigine is to be administered to a patient receiving VPA, lamotrigine must be given at a reduced dosage, less than half the dose used in patients not receiving VPA (see DOSAGE AND ADMINISTRATION and

PRECAUTIONS: Drug Interactions).

Absorption: Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption.

Distribution: Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding: Data from in vitro studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is four to six times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or VPA. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Drug Disposition: Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 μCi) to six healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Enzyme Induction: The effects of lamotrigine on specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $T_{½}$ and a 37% increase in Cl/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by LAMICTAL may not occur when LAMICTAL is given as adjunctive therapy in patients receiving EIAEDs.

Dose Proportionality: In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In two small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

Elimination: (See Table 1)

Special Populations: Patients With Renal Insufficiency: Twelve volunteers with chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another six individuals undergoing hemodialysis were each given a single 100-mg dose of LAMICTAL. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session.

Hepatic Disease*:* The pharmacokinetics of lamotrigine following a single 100-mg dose of LAMICTAL were evaluated in 24 subjects with moderate to severe hepatic dysfunction and compared with 12 subjects without hepatic impairment. The median apparent clearance of lamotrigine was 0.31, 0.24, or 0.10 mL/kg/min in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared to

0.34 mL/kg/min in the healthy controls. Median half-life of lamotrigine was 36, 60, or 110 hours in patients with Grade A, B, or C hepatic impairment, respectively, versus 32 hours in healthy controls.

Age: Pediatric Patients: The pharmacokinetics of LAMICTAL following a single 2-mg/kg dose were evaluated in two studies of pediatric patients with epilepsy (n = 25 for patients aged 10 months to 5.3 years and n = 19 for patients aged 5 to 11 years). All patients were receiving concomitant therapy with other AEDs. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. Weight normalized oral clearance (Cl/F) was higher (onefold to threefold) in infants and children (age 10 months to 11 years) than in the adolescents and adults, while adolescents and adults had similar mean values of Cl/F.

Table 2: Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	t_{max} (h)	$t_{½}$ (h)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA only*	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

*Two subjects were included in the calculation for mean t_{max}.

† Parameter not estimated.

Elderly: In a single-dose study (150 mg of LAMICTAL), the pharmacokinetics of lamotrigine in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range = 33 to 108) were similar to those of young, healthy volunteers in other studies.

Gender: The clearance of lamotrigine is not affected by gender.

Race: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

CLINICAL STUDIES: The results of controlled clinical trials established the efficacy of LAMICTAL as monotherapy in adults with partial onset seizures already receiving treatment with a single enzyme-inducing antiepileptic drug (EIAED), as adjunctive therapy in adults with partial seizures, and as adjunctive therapy in

the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving Treatment With a Single EIAED: The effectiveness of monotherapy with LAMICTAL was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The patients experienced at least four simple partial, complex partial, and/or secondarily generalized seizures during each of two consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or VPA (1000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with LAMICTAL or VPA during the next 4 weeks, then continued on monotherapy for an additional 12-week period.

Study endpoints were completion of all weeks of study treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized-tonic-clonic (GTC) seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentage of patients who met escape criteria was 42% (32/76) in the LAMICTAL group and 69% (55/80) in the VPA group. The difference in the percentage of patients meeting escape criteria was statistically significant ($P = 0.0012$) in favor of LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

Patients in the control group were intentionally treated with a relatively low dose of valproate; as such, the sole objective of this study was to demonstrate the effectiveness and safety of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of LAMICTAL to an adequate dose of valproate.

Adjunctive Therapy With LAMICTAL in Adults: The effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in three multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing therapy. In all three studies, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial seizures in the intent-to-treat population (all patients who received at least one dose of treatment) in each study, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy studies.

One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than two other anticonvulsants and VPA was not allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median reductions in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was statistically significant in the 500-mg/day group compared to the placebo group, but not in the 300-mg/day group.

A second study (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than two other anticonvulsants and VPA was not allowed. The target dose of LAMICTAL was 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median change in seizure frequency was a 25% reduction on LAMICTAL compared to placebo ($P<0.001$).

The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week

treatment periods separated by a 4-week washout period. Patients could not be on more than two other anticonvulsants. Thirteen patients were on concomitant VPA; these patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on LAMICTAL compared to placebo (P<0.01).

No differences in efficacy based on age, sex, or race, as measured by change in seizure frequency, were detected.

Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up to three drugs. Patients were dosed on a fixed-dose regimen based on body weight and VPA use. Target doses were designed to approximate 5 mg/kg per day for patients taking VPA (maximum dose, 200 mg/day) and 15 mg/kg per day for patients not taking VPA (maximum dose, 400 mg/day). The primary efficacy endpoint was median reduction from baseline in major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on placebo, a difference that was statistically significant (P<0.05). Drop attacks were significantly reduced by LAMICTAL (34%) compared to placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo, respectively).

INDICATIONS AND USAGE:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Monotherapy Use: LAMICTAL is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single EIAED.

Safety and effectiveness of LAMICTAL have not been established 1) as initial monotherapy, 2) for conversion to monotherapy from non–enzyme-inducing AEDs (e.g., valproate), or 3) for simultaneous conversion to monotherapy from two or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

Safety and effectiveness in patients below the age of 16 other than those with Lennox-Gastaut syndrome have not been established (see BOX WARNING).

CONTRAINDICATIONS: LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

Serious Rash: ***Pediatric Population:*** The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients was approximately 1.1% (14/1233). When these 14 cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There were no deaths or

permanent sequelae in these patients. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. It bears emphasis, accordingly, that LAMICTAL is only approved for use in those patients below the age of 16 who have seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS).

Because foreign postmarketing reports suggested that the rate of serious rash was greater with concomitant VPA use and because metabolism of LAMICTAL is inhibited by VPA, resulting in increased LAMICTAL plasma levels, the drug development database was examined for concomitant VPA use. In pediatric patients who used VPA concomitantly, 1.1% (5/443) experienced a serious rash compared to 1% (6/628) patients not taking VPA. Although the numbers are small, 1.7% (5/294) patients taking either VPA alone or VPA + non-EIAEDs experienced a serious rash compared to 0% (0/149) patients taking VPA + EIAEDs.

Adult Population: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11/3348) of patients who received LAMICTAL in premarketing clinical trials. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, hematologic, and hepatologic abnormalities.

There is evidence that the inclusion of VPA in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with VPA in clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2398 clinical trial patients and volunteers administered LAMICTAL in the absence of VPA were hospitalized.

Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, one case was reported to be Stevens-Johnson–like.
Hypersensitivity Reactions: Hypersensitivity reactions, some fatal or life threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.
Acute Multiorgan Failure: Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2/3796 adult patients and 3/1136 pediatric patients who received LAMICTAL during premarketing clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, making it difficult to identify the initial cause.

Additionally, three patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in two patients. Both pediatric patients were receiving concomitant therapy with VPA, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

Pure Red Cell Aplasia (PRCA): A case of PRCA was reported in a 32-year-old male with a history of β-thalassemia. The patient had a microcytic anemia (hemoglobin 11 g/dL) that was stable while the patient received carbamazepine but became more severe in the 3 months after LAMICTAL was added. A bone marrow aspirate revealed markedly decreased erythropoiesis but normal granulopoiesis and thrombopoiesis. Erythropoiesis resumed after discontinuation of LAMICTAL and transfusions of packed red cells. Although PRCA is known to occur in patients with hemoglobinopathies, it is not known if β-thalassemia is a specific risk factor for the development of PRCA.

Withdrawal Seizures: As a rule, AEDs should not be abruptly discontinued because of the possibility of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS:

Dermatological Events (see BOX WARNING, WARNINGS): Serious rashes associated with hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have been reported, but their numbers are too few to permit a precise estimate of the rate. There are suggestions, yet to be proven, that the risk of rash may also be increased by 1) coadministration of LAMICTAL with VPA, 2) exceeding the recommended initial dose of LAMICTAL, or 3) exceeding the recommended dose escalation for LAMICTAL. However, cases have been reported in the absence of these factors.

In clinical trials, approximately 10% of all patients exposed to LAMICTAL developed a rash. Rashes associated with LAMICTAL do not appear to have unique identifying features. Typically, rash occurs in the first 2 to 8 weeks following treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although most rashes resolved even with continuation of treatment with LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life threatening. **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**

Sudden Unexplained Death in Epilepsy (SUDEP): During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4700 patients with epilepsy (5747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for LAMICTAL, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving LAMICTAL and those receiving another antiepileptic drug that underwent clinical testing in a similar population at about the same time. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

Status Epilepticus: Valid estimates of the incidence of treatment emergent status epilepticus among patients treated with LAMICTAL are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2343 adult patients had episodes that could

unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Addition of LAMICTAL to a Multidrug Regimen That Includes VPA (Dosage Reduction): Because VPA reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of VPA is less than half of that required in its absence (see DOSAGE AND ADMINISTRATION).

Use in Patients With Concomitant Illness: Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or conditions that could affect metabolism or elimination of the drug, such as renal, hepatic, or cardiac functional impairment.

Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of elimination of lamotrigine (see CLINICAL PHARMACOLOGY).

A study in individuals with severe chronic renal failure (mean creatinine clearance = 13 mL/min) not receiving other AEDs indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with LAMICTAL, it should be used with caution in these patients, generally using a reduced maintenance dose for patients with significant impairment.

Because there is limited experience with the use of LAMICTAL in patients with impaired liver function, the use in such patients may be associated with as yet unrecognized risks (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Binding in the Eye and Other Melanin-Containing Tissues: Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Information for Patients: Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately. In addition, the patient should notify his physician if worsening of seizure control occurs.

Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LAMICTAL. See PATIENT INFORMATION at the end of this labeling for the text of the leaflet provided for patients.

Laboratory Tests: The value of monitoring plasma concentrations of LAMICTAL has not been established. Because of the possible pharmacokinetic interactions between LAMICTAL and other AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of LAMICTAL and concomitant AEDs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other anti-seizure drugs and whether or not dosage adjustments are necessary.

Drug Interactions: ***Antiepileptic Drugs:*** The use of AEDs in combination is complicated by the potential for pharmacokinetic interactions.

The interaction of lamotrigine with phenytoin, carbamazepine, and VPA has been studied. The net effects of these various AED combinations on individual AED plasma concentrations are summarized in Table 3.

Table 3: Summary of AED Interactions With LAMICTAL

AED	AED Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive AEDs†
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide‡	?	
Valproic acid (VPA)	↓	↑
VPA + PHT and/or CBZ	NE	↔

* From adjunctive clinical trials and volunteer studies.

† Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.

‡ Not administered, but an active metabolite of carbamazepine.

↔ = No significant effect.

? = Conflicting data.

NE = Not evaluated.

Specific Effects of Lamotrigine on the Pharmacokinetics of Other AED Products: LAMICTAL Added to Phenytoin: LAMICTAL has no appreciable effect on steady-state phenytoin plasma concentration.

LAMICTAL Added to Carbamazepine: LAMICTAL has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL (see ADVERSE REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels were seen to increase.

LAMICTAL Added to VPA: When LAMICTAL was administered to 18 healthy volunteers receiving VPA in a pharmacokinetic study, the trough steady-state VPA concentrations in plasma decreased by an average of 25% over a 3-week period, and then stabilized. However, adding LAMICTAL to the existing therapy did not cause a change in plasma VPA concentrations in either adult or pediatric patients in controlled clinical trials.

Specific Effects of Other AED Products on the Pharmacokinetics of Lamotrigine: Phenytoin Added to LAMICTAL: The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 45% to 54% depending upon the total daily dose of phenytoin (i.e., from 100 to 400 mg).

Carbamazepine Added to LAMICTAL: The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Phenobarbital or Primidone Added to LAMICTAL: The addition of phenobarbital or primidone decreases lamotrigine steady-state concentrations by approximately 40%.

VPA Added to LAMICTAL: The addition of VPA increases lamotrigine steady-state concentrations in normal volunteers by slightly more than twofold.

Interactions With Drug Products Other Than AEDs: Folate Inhibitors: Lamotrigine is an inhibitor of

dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenicity was seen in one mouse study or two rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for rats, doses that are equivalent to 90 mg/m^2 and 60 to 90 mg/m^2, respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.

Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in two gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In two cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities.

No evidence of impairment of fertility was detected in rats given oral doses of lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg per day or 0.4 times the human dose on a mg/m^2 basis. The effect of lamotrigine on human fertility is unknown.

Pregnancy: Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m^2 basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg per day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg per day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m^2 basis, respectively.

Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m^2 basis.

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m^2 basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all three drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the two highest doses, and occurred between day 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

Although LAMICTAL was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: To facilitate monitoring fetal outcomes of pregnant women exposed to

lamotrigine, physicians are encouraged to register patients, **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known,** and can obtain information by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Labor and Delivery: The effect of LAMICTAL on labor and delivery in humans is unknown.

Use in Nursing Mothers: Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to LAMICTAL by this route are unknown, breast-feeding while taking LAMICTAL is not recommended.

Pediatric Use: In pediatric patients, LAMICTAL is only indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome. Safety and effectiveness for other uses in patients below the age of 16 years have not been established (see BOX WARNING).

Geriatric Use: Because few patients over the age of 65 (approximately 20) were exposed to LAMICTAL during its premarket evaluation, no specific statements about the safety or effectiveness of LAMICTAL in this age-group can be made.

ADVERSE REACTIONS: SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH THERAPY WITH LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE (see BOX WARNING).

Most Common Adverse Events in All Clinical Studies: ***Adjunctive Therapy in Adults:*** The most commonly observed (≥5%) adverse experiences seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant VPA than in patients not receiving VPA (see WARNINGS).

Approximately 11% of the 3378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%).

In a dose response study in adults, the rate of discontinuation of LAMICTAL for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose related.

Monotherapy in Adults: The most commonly observed (≥ 5%) adverse experiences seen in association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥ 5%) adverse experiences associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Lennox-Gastaut Syndrome: The most commonly

observed (≥ 5%) adverse experiences seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients with Lennox-Gastaut syndrome and not seen at an equivalent rate in the control group were pharyngitis, infection, rash, vomiting, bronchitis, accidental injury, constipation, and flu syndrome.

In 169 patients with Lennox-Gastaut syndrome (26 patients were between the ages of 16 and 25), 3.8% of patients on LAMICTAL and 7.8% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL and deterioration of seizure control for patients treated with placebo.

Approximately 10% of the 1136 pediatric patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.9%), reaction aggravated (1.7%), and ataxia (0.9%).

Incidence in Controlled Clinical Studies: The prescriber should be aware that the figures in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Incidence in Controlled Adjunctive Clinical Studies in Adults: Table 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to the patient's current AED therapy. Adverse events were usually mild to moderate in intensity.

Table 4: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials*
(Events in at least 2% of patients treated with LAMICTAL
and numerically more frequent than in the placebo group.)

Body System/ Adverse Experience†	Percent of Patients Receiving Adjunctive LAMICTAL (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
Body as a whole		
Headache	29	19
Flu syndrome	7	6
Fever	6	4
Abdominal pain	5	4
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Tooth disorder	3	2
Anorexia	2	1
Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2
Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0
Concentration disturbance	2	1
Respiratory		
Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		

Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

* Patients in these adjunctive studies were receiving one to three concomitant EIAEDs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

† Adverse experiences reported by at least 2% of patients treated with LAMICTAL are included.

In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL, some of the more common drug-related adverse events were dose related (see Table 5).

Table 5: Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults

	Percent of Patients Experiencing Adverse Experiences		
Adverse Experience	Placebo (n = 73)	LAMICTAL 300 mg (n = 71)	LAMICTAL 500 mg (n = 72)
Ataxia	10	10	28*†
Blurred vision	10	11	25*†
Diplopia	8	24*	49*†
Dizziness	27	31	54*†
Nausea	11	18	25*
Vomiting	4	11	18*

*Significantly greater than placebo group (P<0.05).

†Significantly greater than group receiving LAMICTAL 300 mg (P<0.05).

Other events that occurred in more than 1% of patients but equally or more frequently in the placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia, paresthesia, respiratory disorder, and urinary tract infection.

The overall adverse experience profile for LAMICTAL was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. Generally, females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse experiences than males. The only adverse experience for which the reports on LAMICTAL were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was little difference between females and males in the rates of discontinuation of LAMICTAL for individual adverse

experiences.

Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures: Table 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

Table 6: Treatment-Emergent Adverse Event Incidence in Adults in a Controlled Monotherapy Trial* (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the valproate [VPA] group.)

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL Monotherapy‡ (n = 43)	Percent of Patients Receiving Low-Dose VPA§ Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Asthenia	2	0
Fever	2	0
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Anorexia	2	0
Dry mouth	2	0
Rectal hemorrhage	2	0
Peptic ulcer	2	0
Metabolic and nutritional		
Weight decrease	5	2
Peripheral edema	2	0
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Amnesia	2	0
Ataxia	2	0
Depression	2	0
Hypesthesia	2	0
Libido increase	2	0
Decreased reflexes	2	0
Increased reflexes	2	0
Nystagmus	2	0
Irritability	2	0
Suicidal ideation	2	0
Respiratory		
Rhinitis	7	2
Epistaxis	2	0
Bronchitis	2	0

Dyspnea	2	0
Skin and appendages		
Contact dermatitis	2	0
Dry skin	2	0
Sweating	2	0
Special senses		
Vision abnormality	2	0
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

* Patients in these studies were converted to LAMICTAL or VPA monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.

† Adverse experiences reported by at least 2% of patients are included.

‡ Up to 500 mg/day.

§ 1000 mg/day.

Incidence in a Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome: Table 7 lists adverse events that occurred in at least 2% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg per day. Reported adverse events were classified using COSTART terminology.

Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)

Body System/ Adverse Experience	Percent of Patients Receiving LAMICTAL (n = 79)	Percent of Patients Receiving Placebo (n = 90)
Body as a whole		
Infection	13	8
Accidental injury	9	7
Flu syndrome	5	0
Asthenia	3	1
Abdominal pain	3	0
Cardiovascular		
Hemorrhage	3	0
Digestive		
Vomiting	9	7
Constipation	5	2
Diarrhea	4	2
Nausea	4	1
Anorexia	3	1
Nervous system		
Ataxia	4	1
Convulsions	4	1
Tremor	3	0
Respiratory		
Pharyngitis	14	10
Bronchitis	9	7
Pneumonia	3	0
Skin		
Rash	9	7
Eczema	4	0
Urogenital		
Urinary tract infection	3	0
Balanitis	2	0
Penis disorder	2	0

Other Adverse Events Observed During All Clinical Trials For Adult and Pediatric Patients: LAMICTAL has been administered to 3923 individuals for whom complete adverse event data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a

smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 3923 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Pain. ***Infrequent:*** Accidental injury, allergic reaction, back pain, chills, face edema, halitosis, infection, and malaise. ***Rare:*** Abdomen enlarged, abscess, photosensitivity, and suicide attempt.

Cardiovascular System: Infrequent: Flushing, hot flashes, migraine, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. ***Rare:*** Angina pectoris, atrial fibrillation, deep thrombophlebitis, hemorrhage, hypertension, and myocardial infarction.

Dermatological: Infrequent: Acne, alopecia, dry skin, erythema, hirsutism, maculopapular rash, skin discoloration, Stevens-Johnson syndrome, sweating, urticaria, and vesiculobullous rash. ***Rare:*** Angioedema, erythema multiforme, fungal dermatitis, herpes zoster, leukoderma, petechial rash, pustular rash, and seborrhea.

Digestive System: Infrequent: Dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia, increased appetite, increased salivation, liver function tests abnormal, mouth ulceration, stomatitis, thirst, and tooth disorder. ***Rare:*** Eructation, gastritis, gastrointestinal hemorrhage, gum hemorrhage, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, and tongue edema.

Endocrine System: Rare: Goiter and hypothyroidism.

Hematologic and Lymphatic System: Infrequent: Anemia, ecchymosis, leukocytosis, leukopenia, lymphadenopathy, and petechia. ***Rare:*** Eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, lymphocytosis, macrocytic anemia, and thrombocytopenia.

Metabolic and Nutritional Disorders: Infrequent: Peripheral edema, weight gain, and weight loss. ***Rare:*** Alcohol intolerance, alkaline phosphatase increase, bilirubinemia, general edema, and hyperglycemia.

Musculoskeletal System: Infrequent: Joint disorder, myasthenia, and twitching. ***Rare:*** Arthritis, bursitis, leg cramps, pathological fracture, and tendinous contracture.

Nervous System: Frequent: Amnesia, confusion, hostility, memory decrease, nervousness, nystagmus, thinking abnormality, and vertigo. ***Infrequent:*** Abnormal dreams, abnormal gait, agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal convulsions, hallucinations, hyperkinesia, hypertonia, hypesthesia, libido increased, mind racing, muscle spasm, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, and stupor. ***Rare:*** Cerebrovascular accident, cerebellar syndrome, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, hemiplegia, hyperalgesia, hyperesthesia, hypoesthesia, hypokinesia, hypomania, hypotonia, libido decreased, manic depression reaction, movement disorder, neuralgia, neurosis, paralysis, and suicidal ideation.

Respiratory System: Infrequent: Dyspnea, epistaxis, and hyperventilation. ***Rare:*** Bronchospasm, hiccup, and sinusitis.

Special Senses: Infrequent: Abnormality of accommodation, conjunctivitis, ear pain, oscillopsia, photophobia, taste perversion, and tinnitus. ***Rare:*** Deafness, dry eyes, lacrimation disorder, parosmia, ptosis, strabismus, taste loss, and uveitis.

Urogenital System: Infrequent: Female lactation, hematuria, polyuria, urinary frequency, urinary

incontinence, urinary retention, and vaginal moniliasis. ***Rare:*** Abnormal ejaculation, acute kidney failure, breast abscess, breast neoplasm, breast pain, creatinine increase, cystitis, dysuria, epididymitis, impotence, kidney failure, kidney pain, menorrhagia, and urine abnormality.

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

Blood and Lymphatic: Agranulocytosis, aplastic anemia, disseminated intravascular coagulation, hemolytic anemia,neutropenia, pancytopenia, red cell aplasia.

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Neurology: Exacerbation of parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.

Non-site Specific: Hypersensitivity reaction, multiorgan failure, progressive immunosuppression.

DRUG ABUSE AND DEPENDENCE: The abuse and dependence potential of LAMICTAL have not been evaluated in human studies.

OVERDOSAGE:

Human Overdose Experience: Overdoses involving quantities up to 15 g have been reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

Management of Overdose: There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL.

DOSAGE AND ADMINISTRATION:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Monotherapy Use: LAMICTAL is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single EIAED (e.g., carbamazepine, phenytoin, phenobarbital, etc.).

Safety and effectiveness of LAMICTAL have not been established 1) as initial monotherapy, 2) for conversion to monotherapy from non–enzyme-inducing AEDs (e.g., valproate), or 3) for simultaneous conversion to monotherapy from two or more concomitant AEDs.

Safety and effectiveness in pediatric patients below the age of 16 years other than those with Lennox-Gastaut syndrome have not been established (see BOX WARNING).

General Dosing Considerations: The risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven,

that the risk of severe, potentially life-threatening rash may be increased by 1) coadministration of LAMICTAL with valproic acid (VPA), 2) exceeding the recommended initial dose of LAMICTAL, or 3) exceeding the recommended dose escalation for LAMICTAL. However, cases have been reported in the absence of these factors (see BOX WARNING). Therefore, it is important that the dosing recommendations be followed closely.

Adjunctive Therapy With LAMICTAL: This section provides specific dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of age. Within each of these age-groups, specific dosing recommendations are provided depending upon whether or not the patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years of age, Tables 10 and 11 for patients greater than 12 years of age). In addition, the section provides a discussion of dosing for those patients receiving concomitant AEDs that have not been systematically evaluated in combination with LAMICTAL.

For dosing guidelines for LAMICTAL below, enzyme-inducing antiepileptic drugs (EIAEDs) include phenytoin, carbamazepine, phenobarbital, and primidone.

Patients 2 to 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to an antiepileptic drug (AED) regimen containing VPA are summarized in Table 8. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 9.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

Note that the starting doses and dose escalations listed below are different than those used in clinical trials; however, the maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestions that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. It is likely that patients aged 2 to 6 years will require a maintenance dose at the higher end of the maintenance dose range.

The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg, and only whole tablets should be administered. If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet (see HOW SUPPLIED and PATIENT INFORMATION for a description of the LAMICTAL Chewable Dispersible Tablet available sizes).

Table 8: LAMICTAL Added to an AED Regimen Containing VPA in Patients 2 to 12 Years of Age

Weeks 1 and 2		0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of Lamictal 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every *other* day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.			

Table 9: LAMICTAL Added to EIAEDs (Without VPA) in Patients 2 to 12 Years of Age

Weeks 1 and 2	0.6 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.
Weeks 3 and 4	1.2 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	

Patients Over 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to VPA are summarized in Table 10. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 11.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

Table 10: LAMICTAL Added to an AED Regimen Containing VPA in Patients Over 12 Years of Age

Weeks 1 and 2	25 mg every *other* day
Weeks 3 and 4	25 mg every day
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses). To achieve maintenance, doses may be increased by 25 to 50 mg/day every 1 to 2 weeks. The usual maintenance dose in patients adding LAMICTAL to VPA alone ranges from 100 to 200 mg/day.	

Table 11: LAMICTAL Added to EIAEDs (Without VPA) in Patients Over 12 Years of Age

Weeks 1 and 2	50 mg/day
Weeks 3 and 4	100 mg/day in two divided doses
Usual maintenance dose: 300 to 500 mg/day (in two divided doses). To achieve maintenance, doses may be increased by 100 mg/day every 1 to 2 weeks.	

Conversion From a Single EIAED to Monotherapy With LAMICTAL in Patients ≥16 Years of Age: The goal of the transition regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of LAMICTAL.

The conversion regimen involves two steps. In the first, LAMICTAL is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually withdrawn over a period of 4 weeks.

The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in two divided doses.

LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the guidelines in Table 11 above. The regimen for the withdrawal of the concomitant EIAED is based on experience gained in the controlled monotherapy clinical trial. In that trial, the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.

Because of an increased risk of rash, the recommended initial dose and subsequent dose escalations of LAMICTAL should not be exceeded (see BOX WARNING).

Usual Maintenance Dose: The usual maintenance doses identified in the tables above are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug regimens employing EIAEDs **without VPA**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving **VPA alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in the tables above has not been established in controlled trials.

Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with moderate to severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

Patients With Renal Functional Impairment: Initial doses of LAMICTAL should be based on patients' AED regimen (see above); reduced maintenance doses may be effective for patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY). Few patients with severe renal impairment have

been evaluated during chronic treatment with LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be used with caution in these patients.

Discontinuation Strategy: For patients receiving LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed.

If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal (see PRECAUTIONS).

Discontinuing an EIAED should prolong the half-life of lamotrigine; discontinuing VPA should shorten the half-life of lamotrigine.

Target Plasma Levels: A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response.

Administration of LAMICTAL Chewable Dispersible Tablets: LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. *No attempt should be made to administer partial quantities of the dispersed tablets.*

HOW SUPPLIED: LAMICTAL Tablets, 25 mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100 (NDC 0173-0633-02).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place.

LAMICTAL Tablets, 100 mg, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100 (NDC 0173-0642-55).

LAMICTAL Tablets, 150 mg, cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60 (NDC 0173-0643-60).

LAMICTAL Tablets, 200 mg, blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60 (NDC 0173-0644-60).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

LAMICTAL Chewable Dispersible Tablets, 2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30 (NDC 0173-0699-00). ORDER DIRECTLY FROM GLAXO WELLCOME, INC. 1-800-334-4153.

LAMICTAL Chewable Dispersible Tablets, 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100 (NDC 0173-0526-00).

LAMICTAL Chewable Dispersible Tablets, 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100 (NDC 0173-0527-00).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place.

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

PATIENT INFORMATION: The following wording is contained in a separate leaflet provided for patients.

Information for the Patient

LAMICTAL® (lamotrigine) Tablets

 **25 mg, white** **Imprinted with** **LAMICTAL 25**	 **100 mg, peach** **Imprinted with** **LAMICTAL 100**	 **150 mg, cream** **Imprinted with** **LAMICTAL 150**	 **200 mg, blue** **Imprinted with** **LAMICTAL 200**

LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

 **2 mg, white** **Imprinted with** **LTG 2**	 **5 mg, white** **Imprinted with** **GX CL2**	 **25 mg, white** **Imprinted with** **GX CL5**

NOTE: The pictures above show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable Dispersible Tablets. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

Please read this leaflet carefully before you take LAMICTAL and read the leaflet provided with any refill, in case any information has changed. This leaflet provides a summary of the information about your medicine. Please do not throw away this leaflet until you have finished your medicine. This leaflet does not contain all the information about LAMICTAL and is not meant to take the place of talking with your doctor. If you have any questions about LAMICTAL, ask your doctor or pharmacist.

Information About Your Medicine*:*

The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is one that you and your doctor should make together.

1. The Purpose of Your Medicine:

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

2. Who Should Not Take LAMICTAL:

You should not take LAMICTAL if you had an allergic reaction to it in the past.

3. Side Effects to Watch for:

- Most people who take LAMICTAL tolerate it well. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and

rash.

- Although most patients who develop rash while receiving LAMICTAL have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children than in adults.
- Rashes may be more likely to occur if you: 1) take LAMICTAL in combination with valproic acid (DEPAKENE® or DEPAKOTE®), 2) take a higher starting dose of LAMICTAL than your doctor prescribed, or 3) increase your dose of LAMICTAL faster than prescribed.
- It is not possible to predict whether a mild rash will develop into a more serious reaction. **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. A doctor should evaluate your condition and decide if you should continue taking LAMICTAL**.

4. The Use of LAMICTAL During Pregnancy and Breast-feeding:

The effects of LAMICTAL during pregnancy are not known at this time. If you are pregnant or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you should discuss this with your doctor to determine if you should continue to take LAMICTAL.

5. How to Use LAMICTAL:

- It is important to take LAMICTAL exactly as instructed by your doctor. The dose of LAMICTAL must be increased slowly. It may take several weeks or months before your final dosage can be determined by your doctor, based on your response.
- Do not increase your dose of LAMICTAL or take more frequent doses than those indicated by your doctor.
- If you miss a dose of LAMICTAL, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other seizure medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

6. How to Take LAMICTAL:

LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

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7. Storing Your Medicine:

Store LAMICTAL at room temperature away from heat and light. Always keep your medicines out of the reach of children.

This medicine was prescribed for your use only to treat seizures. Do not give the drug to others.

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

US Patent No. 4,602,017 and 5,698,226

September 2000 RL-860

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Information for the Patient

LAMICTAL® (lamotrigine) Tablets

			
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LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

		
2 mg, white Imprinted with LTG 2	**5 mg, white Imprinted with GX CL2**	**25 mg, white Imprinted with GX CL5**

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- If you miss a dose of lamotrigine, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other seizure medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.
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To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire amount immediately.

7. Storing Your Medicine:

Store LAMICTAL at room temperature away from heat and light. Always keep your medicines out of the reach of children.

This medicine was prescribed for your use only to treat seizures. Do not give the drug to others.

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

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US Patent No. 4,602,017 and 5,698,226

September 2000 RL-860